Methoxyflurane toxicity: historical determination and lessons for modern patient and occupational exposure

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ABSTRACT

AIM: Historically methoxyflurane was used for anaesthesia. Evidence of nephrotoxicity led to abandonment of this application. Subsequently, methoxyflurane, in lower doses, has re-emerged as an analgesic agent, typically used via the Penthrox inhaler in the ambulance setting. We review the literature to consider patient and occupational risks for methoxyflurane.

METHOD: Articles were located via PubMed, ScienceDirect, Google Scholar, *Anesthesiology* journal and the Cochrane Library.

RESULTS: Early studies investigated pharmacokinetics and considered the resulting effects to pose minimal risk. Pre-clinical rodent studies utilised a species not vulnerable to the nephrotoxic fluoride metabolite of methoxyflurane, so nephrotoxicity was not identified until almost a decade after its introduction, and was initially met with scepticism. Further evidence of nephrotoxicity led to abandonment of methoxyflurane use for anaesthesia. Subsequent research suggested there are additional risks potentially relevant to recurrent patient or occupational exposure. Specifically, greater than expected fluoride production after repeated low-dose exposure, increased fluoride production due to medication-caused hepatic enzyme induction, fluoride deposition in bone potentially acting as a slow-release fluoride compartment, which suggests a risk of skeletal fluorosis, and hepatotoxicity. Gestational risk is unclear.

CONCLUSIONS: Methoxyflurane poses a potentially substantial health risk in high (anaesthetic) doses, and there are a number of pathways whereby repeated exposure to methoxyflurane in lower doses may pose a risk. Single analgesic doses in modern use generally appear safe for patients. However, the safety of recurrent patient or occupational healthcare-worker exposure has not been confirmed, and merits further investigation.

Methoxyflurane is a volatile organic liquid,[1] a fluorinated hydrocarbon, that vaporises readily[2] and has historically been used as an anaesthetic agent from 1958.[3] A decade after discovery, methoxyflurane was used frequently, making up 10% of annual purchases of inhaled anaesthetics in the USA.[3] Sedative and analgesic effects were described,[4,5] which prompted an extension of its use outside of the operating room for indications such as labour pain[6–8] and dressing changes.[9]

Renal failure was identified in some patients anaesthetised with methoxyflurane.[10,11] Methoxyflurane is estimated to have been responsible for clinical nephrotoxicity in approximately 100 patients worldwide, and death in approximately 20 cases, before its near universal discontinuation since the 1970s.[12]

However, methoxyflurane has been reintroduced into the contemporary armamentarium as an analgesic for emergency or short procedures. Australasia,[13,14] Europe,[15]

Canada,[16] South Africa[17] and, more recently, numerous other countries[18] allow methoxyflurane administration via the Penthrox inhaler. This device has been manufactured by Medical Developments International (formerly Medical Developments Australia) since 1978, specifically for analgesic use,[19] and Penthrox is currently the only widely commercially available methoxyflurane administration device. The Penthrox inhaler is a tube into which the methoxyflurane medication is poured to soak a wick, with a whistle-like mouthpiece through which the patient inhales methoxyflurane vapour.[20] The device features a 'dilution hole', which allows the patient to control the concentration delivered[18,21] and can incorporate an activated carbon (AC) filter through which the patient is encouraged to exhale. Methoxyflurane has an estimated atmospheric lifetime of 54 days and a 100-year global warming potential four times that of carbon dioxide, although it compares favourably in that regard against other inhalational anaesthetics.[22] Administration of methoxyflurane via the Penthrox inhaler has been demonstrated as more effective at relieving pain than placebos and alternative analgesia in a variety of settings including pre-hospital,[23,24] clinic,[25] and emergency department.[26,27]

We reviewed the historic literature to describe the evolution in the understanding of the health risks associated with anaesthetic methoxyflurane. Thus we identify the potential patient and occupational risks of methoxyflurane in the modern setting, in order to help guide policymakers and clinicians who might consider making methoxyflurane available in their clinical environments.

Search strategy

To gain a comprehensive overview of the historical literature, we sought to locate research and commentary on methoxyflurane administration in any setting for any indication by any method other than the modern Penthrox inhaler. Articles were located using PubMed, ScienceDirect and Google Scholar and by searching the *Anesthesiology* journal and Cochrane Library databases with the term 'methoxyflurane'. Articles were selected based on relevance to health effects, as categorised in the following sections of this paper. Only English-language material was reviewed. Reference sections of relevant articles were examined to identify further relevant material for inclusion. Documents included in this review range across case reports, animal and human prospective observational studies, experimental trials and other literature reviews.

Historic use of methoxyflurane

Early published animal studies were conducted on dogs and determined that, with regards to incidence of lethal arrhythmias,[29,30] electrolyte disturbances or liver dysfunction,[31] methoxyflurane compared favourably with alternative inhaled anaesthetic agents. Reports were conflicted with regards to cardiovascular and respiratory effects,[31–33] although these risks are not generally discussed in later investigations. Researchers of canine models noted a slow recovery from anaesthesia, with the dogs appearing sluggish until the next day.[31] Anaesthetised human subjects also exhibited slow onset and emergence from anaesthesia.[4] Arterial methoxyflurane was approximately double the venous level during early anaesthesia (2 to 15 minutes), equilibrating after 100 minutes.[34] This suggests ready uptake into tissue, confirming laboratory studies that had suggested methoxyflurane would have high solubility in blood and high uptake in adipose tissue.[28] Methoxyflurane concentration in subcutaneous fat rose slowly, peaking 5–8 hours after commencement of anaesthesia and remaining elevated beyond 30 hours after cessation.[34] Overall, these studies suggested that methoxyflurane had a large volume of distribution and consequent delayed equilibration between compartments.

As methoxyflurane was a new anaesthetic agent, a significant proportion of the historical animal and human research was dedicated to investigating the rate of onset of and emergence from anaesthesia,[4,31,35,36] the concentration required to achieve adequate anaesthesia[1,20,37] and the threshold of sedation.[36] Early medication safety investigations included effects on respiration[2,4,31,35,38] and cardiovascular stability,[4,35,38,39] with

methoxyflurane demonstrating reasonable safety with regards to these concerns. Although many of these historical anaesthesia studies might not meet modern scientific standards due to the poor quality and quantity of data, examination of this literature nonetheless allows identification and extraction of worthwhile findings.

Fluoride-associated health effects

Methoxyflurane is metabolised by lung and liver tissue into a variety of products,[40] including fluoride and oxalic acid.[20] Some medications are known to increase ('induce') metabolism pathways in the liver. Pre-treatment of rat hepatic microsomes *in vitro* with phenobarbital, an anticonvulsant therapy,[41] caused a 7- to 10-fold increase in fluoride production in response to methoxyflurane exposure.[40,42] Similarly, *in vivo* pre-treatment of rats with phenobarbital increased methoxyflurane uptake and fluoride production.[43–45] A patient who had secobarbital prior to receiving methoxyflurane had peak serum fluoride that was three times that of patients who did not receive secobarbital, and the patient subsequently exhibited a decrease in renal function. This suggests increased risk of elevated serum fluoride, and possibly increased susceptibility to health effects associated with elevated fluoride levels, for exposed individuals concomitantly using medications that affect methoxyflurane metabolism.

Prolonged exposure to methoxyflurane also causes enzyme induction, altering methoxyflurane metabolism.[46] Rat hepatic microsomes *in vitro* exposed to low-dose methoxyflurane produced proportionally more fluoride than with high-dose exposure,[42] and the susceptible Fischer 344 rat strain demonstrated prolonged low-dose exposure also resulting in increased fluoride production.[47] This nonlinear response suggests extrapolation from single high-dose outcomes to repeated low-dose use or occupational exposure [48–50] cannot be undertaken with simple linear assumptions.

Renal toxicity

Although preclinical trials conducted in Sprague-Dawley rats found no evidence of nephrotoxicity,[51] over a decade later it was determined that different rat types exhibited different degrees of hepatic conversion of methoxyflurane into fluoride. Only Fischer 344 rats demonstrated biochemical and pathological renal changes following methoxyflurane anaesthesia.[51] In susceptible rats, elevated fluoride was associated with dose-related high-output renal failure.[43,52,53] Therefore, due to the use of a non-susceptible rat type, preclinical trials had unfortunately failed to identify the nephrotoxic potential of methoxyflurane.

Early observations of anaesthetised human subjects also suggested no renal toxicity.[35] Nephrotoxicity in clinical use was suggested by a 1966 case series of 17 patients,[10] although unfortunately this first report of human methoxyflurane anaesthesia-associated nephrotoxicity was met with scepticism.[12] It was a further five years until further incidents of high-output failure were described,[54–56] at which time a relationship was identified between serum fluoride following methoxyflurane anaesthesia and the degree of renal toxicity. In 1973, strong correlations were identified between methoxyflurane anaesthetic dose, increased serum inorganic fluoride concentration and the degree of nephrotoxicity,[11] with further biochemical evidence of renal dysfunction emerging the following year from patients receiving methoxyflurane anaesthesia.[39,60] Two types of methoxyflurane-induced renal pathology were identified: low output failure exhibited calcium oxalate crystals in the tubules of the renal cortex and the collecting tubules of the medulla, with cortex tubular inflammatory changes;[61] whereas high output failure exhibited tubular necrosis,[51] widespread tubular dilatation and calcium and calcium oxalate crystals in the tubular epithelium.[62] In combination, these findings provided "compelling scientific evidence [which] led practitioners and the manufacturer to abandon methoxyflurane."[12] Methoxyflurane administration to human patients for both anaesthesia and analgesia was generally discontinued around 1974.[19,63]

There appears to be inter-person variation in response to serum fluoride resulting from methoxyflurane, with some studies demonstrating serum fluoride levels above the toxic threshold[11] without identifying renal dysfunction.[65,66] This variability may be partially explained by additive nephrotox-

icity from medications, such as tetracycline or other antibiotics,[67,68] that can alter typical methoxyflurane dose-responses, although variable susceptibility to the effects of fluoride and/or other metabolites is also a possibility.

Interestingly, the renal toxic serum fluoride threshold is not necessarily consistent across fluorinated anaesthetic agents.[71–73] For example, sevoflurane, which undergoes minimal renal defluorination compared with methoxyflurane, sometimes produces serum fluoride ≥50μmol/L without apparent renal dysfunction.[71] Transient changes in renal function have been observed in some studies using rats and human subjects following sevoflurane anaesthesia. The renal changes are believed to be due to a different compound that is formed by sevoflurane and unrelated to fluoride formation.[74] However, differences in renal function following sevoflurane are not statistically significant on meta-analysis.[75] It has been suggested that the more pronounced renal metabolism exhibited by methoxyflurane is responsible for its comparatively greater renal toxic effect.[70,71] Direct comparison between agents is challenging.

Fluoride bone deposition

A 1973 study of mice and Wistar rats found 4.7–6.7% of the fluoride in methoxyflurane was deposited in bone. Washout of bone fluoride was slow, returning to control after 40–60 days. In concert with the findings of enzyme induction studies,[40,42] phenobarbital increased the amount of fluoride deposited in bone.[77] Subsequent research confirmed fluoride deposition in rat bone following methoxyflurane anaesthesia, with preferential deposition in foetal bone in the third trimester of pregnancy.[78] Similarly, recurrent high-dose exposure appears to cause decreased foetal ossification and minor skeletal abnormalities in mice.[79]

These findings suggest that bone has the potential to act as a long-acting storage compartment of fluoride metabolite, which raises the possibility of fluoride accumulation with repeated exposure within an extended clearance time frame. Elevated fluoride intake is associated with both elevated serum fluoride and increased skeletal fluorosis risk,[80,81] suggesting the potential for skeletal fluorosis in exposed persons or the foetuses of exposed pregnant persons. However, the quantity of risk is unclear in the context of modern analgesic use and occupational exposure, and further study is needed.

Gestational effects

In rats, recurrent subanaesthetic methoxyflurane exposure does not appear to significantly alter foetal loss, but it does decrease foetal weight.[82] In mice, recurrent low-dose exposure to methoxyflurane provokes increased rates of foetal development variation, and frequent higher-dose (though still subanaesthetic) exposure causes decreased birth weight and increased rates of death *in utero*.[79] These findings suggest that there are potentially gestational effects consequent of recurrent maternal exposure, although large human cohort studies are needed to examine whether such effects occur with modern use.

Women in labour receiving methoxyflurane analgesia during labour produce fluoride that appears in their urine and the urine of their newborns.[83,84] The biological effect of maternal methoxyflurane analgesia on newborns has not been studied in humans. Likewise, human antenatal methoxyflurane use does not appear to have been explicitly studied.[85] Furthermore, there appears to be an absence of research of the occupational safety of pregnant healthcare workers exposed to methoxyflurane.

Hepatotoxicity

Researchers in 1962 noted no clinical indications of liver toxicity in two patient cohorts anaesthetised with methoxyflurane.[35,38] However, subsequent case reports of hepatitis emerged, which were associated with anaesthesia,[86] delivery[7,8] and medication abuse.[87] The majority of these reports occurred as or after methoxyflurane was becoming used less frequently worldwide. A further study in 1980 identified changes in hepatic function biomarkers following occupational exposure of delivery-ward personnel.[88] Hepatotoxicity appears to have been an infrequent but important effect that was unpredictably associated with single or multiple doses of methoxyflurane.

Summary of historical use

In the 1960s, methoxyflurane was a new anaesthetic agent. Research focused on determining its pharmacokinetics, utility as an anaesthetic agent, respiratory effects and cardiovascular changes. None of these factors were ultimately determined to be areas of significant risk. Methoxyflurane appeared to be a useful agent for providing stable anaesthesia with gradual emergence.

Nephrotoxicity was only identified after approximately a decade of use and was not formally associated as a methoxyflurane dose-response until approximately 15 years after its introduction. Individual variation in nephrotoxic threshold added further complication, and it is possible scepticism may have impeded research into toxic effects. Hepatotoxicity occurred infrequently enough that it was not identified as an important risk of methoxyflurane, and the combination of circumstances under which methoxyflurane causes hepatitis are still unclear.

Studies of hepatic induction of methoxyflurane metabolism suggest that frequent low-dose uses or exposures, or some medications taken concomitantly, have the potential to produce proportionally greater toxicity than historical one-off high dose exposures. Bone fluoride deposition as a result of methoxyflurane exposure has been minimally studied. A small but not irrelevant teratogenic risk is suggested by two animal studies undertaken after methoxyflurane use had generally ceased.

Relevance to the modern setting

This review was undertaken with the goal of including the widest possible range of historical literature in order to describe the evolution of understanding of the health risks associated with methoxyflurane. Literature was located non-systematically, including extensive use of locating citations and a wide range of search terms. Thus, the review search is not completely systematic, but it is nonetheless comprehensive. Equally, due to near-global abandonment of studies in the 1970s, research was restricted until recently, which limits numbers and availability of prior publications. Much of the historical data utilise small samples and lack a control group, but nonetheless it is highly unlikely that anaesthetic methoxyflurane studies will ever be repeated to ensure scientific rigour.

Methoxyflurane is experiencing a revival in lower-dose analgesic use. The historical experience has provided some insight into risk in the modern setting, with researchers specifically investigating the possibility and finding no evidence of patient nephrotoxicity and hepatotoxicity in current use.[27,89] However, the literature suggests some unresolved safety concerns.

The Australian Therapeutic Goods Administration (TGA) reported 25 cases of adverse reaction associated with Penthrox between 1971 and 19 July 2020. These cases included two deaths and one report of adverse effect due to occupational exposure.[90] The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) reported six cases of adverse reaction associated with Penthrox between 2000 and 19 October 2020, with no deaths.[91] These reports are aggregated in Table 1. The earliest report in the Australian TGA database is November 2005, and the earliest report in the New Zealand Medsafe database is January 2012. Hence it is possible that any earlier events were unreported.[90,91] It is important to acknowledge that association with adverse events does not necessarily imply methoxyflurane caused the event. However, these reports suggest a non-zero risk requiring surveillance and investigation.

In contemporary use in Australasia, patients are administered up to 6mL methoxyflurane per day and up to 15mL per week.[13,14] Each 3mL dose lasts between 20 and 60 minutes depending on how intensely the patient inhales.[92] Methoxyflurane is used by Australian and New Zealand ambulance services,[23,24,48,89,92–99] by at least one Australian emergency department[100] and in Australasian in-hospital and clinic settings.[25,101–108] It has been administered to five million patients in Australia[18] and a further one million patients outside of Australia.[112] Given this extensive use, the number of adverse events reported is reassuringly low, and suggests that modern use of methoxyflurane may be safe for short-term administration. Furthermore, the low rate of adverse effects implies relative safety for those who are occupationally exposed to methoxyflurane.

Table 1: Aggregated reports of adverse events involving methoxyflurane from the Australian Therapeutic Goods Administration (TGA)[90] and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).[91]

Month Year	Country	Gender	Age	Adverse effects	Other suspected medications	Other concomitant/not suspected medications
Apr 1985	Australia	Male	20	Hepatitis	Chlorpromazine, fentanyl, halothane, flucoxacillin, pancuronium, suxamethonium, pethidine, thiopentone	None reported
Dec 2000	Australia	Male	30	Malignant hyperthermia	Suxamethonium, sevoflurane, propofol	None reported
Nov 2005	Australia	Male	57	Hypoxia, medication error	None reported	None reported
Dec 2005	Australia	Female	34	Confusion, dizziness, hypoxia, somnolence	None reported	None reported
Jun 2006	Australia	Female	20	Jaundice, abnormal liver function test result, vomiting	None reported	None reported
Mar 2008	Australia	Male	26	Blood pressure fluctuation	None reported	None reported
Feb 2010	Australia	Female	33	Hepatitis, hepatomegaly, jaundice, liver injury	None reported	Sodium tetradecyl sulphate, fexofenadine, paracetamol
Feb 2010	Australia	Female	Not reported	Hepatic failure, renal failure	None reported	None reported
Jul 2010	Australia	Male	19	Affect lability, amnesia	None reported	None reported
May 2011	Australia	Female	12	Lipase increased, pancreatitis	Box jellyfish antivenom, morphine, fentanyl	Paracetamol, prednisolone
Nov 2011	Australia	Female	75	Altered state of consciousness, nausea, vomiting	Morphine	Not suspected
Jan 2012	New Zealand	Male	64	Hepatic failure	None reported	None reported

Table 1: Aggregated reports of adverse events involving methoxyflurane from the Australian Therapeutic Goods Administration (TGA)[90] and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) (continued).[91]

Month Year	Country	Gender	Age	Adverse effects	Other suspected medications	Other concomitant/not suspected medications
May 2014	Australia	Female	86	Anaphylactic reaction	Fentanyl, telmisartan	None reported
Apr 2015	Australia	Female	Not reported	Liver function test increased	None reported	None reported
May 2015	Australia	Male	64	Cardiac arrest, hypotension, nausea, syncope	None reported	None reported
Apr 2016	Australia	Male	30	Depressed mood, feeling abnormal, nightmare	None reported	None reported
Jul 2016	Australia	Female	10	Vomiting	Oxycodone, fentanyl, ampicillin	Metronidazole, Augmentin, paracetamol
Sep 2017	New Zealand	Male	36	Dizziness, malaise, nausea	None reported	None reported
May 2018	Australia	Female	47	Dizziness, muscle rigidity, nausea, unresponsive to stimuli	None reported	None reported
Aug 2018	Australia	Male	Not reported	Depressed level of consciousness	None reported	None reported
Aug 2018	New Zealand	Male	11	Abnormal behaviour, depressed level of consciousness, dysphemia, hyperaesthesia, myoclonus	None reported	Morphine
Oct 2018	Australia	Male	Not reported	Drug abuse, hepatitis	None reported	None reported
Feb 2019	Australia	Female	Not reported	Dizziness, occupational exposure to product	None reported	Not reported
May 2019	Australia	Female	48	Aggression, amnesia	None reported	None reported

Table 1: Aggregated reports of adverse events involving methoxyflurane from the Australian Therapeutic Goods Administration (TGA)[90] and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) (continued).[91]

Month Year	Country	Gender	Age	Adverse effects	Other suspected medications	Other concomitant/not suspected medications
Jun 2019	Australia	Female	36	Abdominal pain, hepatitis, liver function test increased, malaise	None reported	None reported
Jul 2019	Australia	Female	Not reported	Intentional product misuse	None reported	None reported
Aug 2019	Australia	Female	75	Aphasia	None reported	None reported
Aug 2019	New Zealand	Female	29	Anaphylactic reaction	Ibuprofen, paracetamol	None reported
Sep 2019	Australia	Male	Not reported	Nephropathy	None reported	None reported
Feb 2020	New Zealand	Female	44	Anaphylactic reaction	None reported	Ethinylestradiol, felodipine, enalapril, citalopram
May 2020	New Zealand	Female	63	Hepatitis, hyperbilirubinaemia, myocardial infarction	None reported	Pantoprazole

However, absence of evidence does not necessarily mean an absence of harm, and it may be difficult to identify the true risk. The identification of potential nephrotoxic and other risks, combined with the low numbers and high age of prior studies, provides a basis for consideration of research of methoxyflurane safety in the modern setting. The literature illustrates a paucity of clinical trials confirming the safety of methoxyflurane in cases other than one-off analgesic administration. Therefore, despite the apparent relative safety in modern use thus far, there is good cause for further research to be undertaken to ensure the safety of patients and healthcare workers.

In summary, the risks of patient and occupational methoxyflurane exposure have been identified. The degree of risk for patients and healthcare workers appears low, but nonetheless remains unquantified in the following domains:

- renal toxicity
- enzyme induction due to concomitant medication use or repeated methoxyflurane exposure
- a possibility of fluoride bone deposition with unknown skeletal fluorosis risk
- hepatotoxicity.

Additionally, there is a notable dearth of research of gestational effects relating to repeated methoxyflurane exposure. Because of these currently unquantified risks, it may be prudent for healthcare workers to minimise exposure through adequate environment ventilation and by directing patients to exhale through the AC filter of the Penthrox device.

A number of areas for future research are suggested. For example, prolonged compartmental equilibration[28,34] suggests a potential for healthcare workers to accumulate methoxyflurane and metabolites with repeated exposure over prolonged periods. Whether such an effect occurs has been investigated only by one pilot study,[113] and further research is warranted. The rate of use among both patients and healthcare workers of relevant enzyme-inducing and nephrotoxic medications could be considered in the context of the increased risk posed by concomitant methoxyflurane use or exposure. Skeletal fluorosis, gestational and hepatotoxic risk should be further investigated. Workplaces where methoxyflurane vapour is present could institute monitoring of at-risk healthcare workers' urine fluoride against published guidelines[114,115] as a general health measure. Although the historical literature associates serum fluoride level with renal toxicity, Safe Work Australia does not recommend workplaces institute serum fluoride testing, due to practical complexities.[115]

Although there has been some primary[108,116] and secondary[48] reporting of occupational exposure ranges with the Penthrox inhaler, the degree to which patients exhale methoxyflurane into the local environment beyond the duration of their treatment could be explained further as this might cause exposure for other healthcare workers who subsequently receive and care for the patient. A recent study supported by the Penthrox manufacturer derived an eight-hour Maximum Exposure Limit by estimating the level at which there is a 10% increased risk of kidney toxicity from historical single-exposure anaesthetic data.[48] This provides a useful measure against which to compare reported or predicted exposures. However, independent confirmation of this Maximum Exposure Limit would be ideal.[48,117,118] Finally, the only recently published determinations of occupational health risk have been theoretical models and extrapolation to compare with a single-exposure nephrotoxic threshold.[48–50] Further research to determine the nephrotoxic and other health effect risk associated with recurrent exposure would be valuable. The historical literature has been examined and the evolution of understanding of health risks associated with methoxyflurane described. This stands as a case study of a medication enthusiastically put into clinical practice without sufficient confirmation of occupational safety. Policymakers should take heed of the persistent need for scientific confirmation of the occupational safety of methoxyflurane administration, and also of the potential for similar oversights that could occur with the utilisation of new medications or medications with controversial characteristics.

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